ZIMANAC EYE DROPS
(Diclofenac Eye Drops 0.1%)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

ZIMANAC EYE DROPS

(Diclofenac Eye Drops 0.1%)

2. Qualitative and quantitative composition

Diclofenac Sodium BP 0.1%

Sorbic Acid BP 0.2% (As preservative)

3. Pharmaceutical form

Eye Drops

4. Clinical particulars

4.1 Therapeutic indications

- Post-operative inflammation in cataract surgery and other surgical interventions.
- Prevention of cystoid macular oedema after cataract extraction with lens implantation.
- Post-traumatic inflammation in non-penetrating wounds.
- Inhibition of miosis in cataract surgery.
- Relief of pain and photophobia.
- Non-infected inflammatory conditions of the anterior segment of the eye.

4.2 Posology and method of administration

Adults

- Ocular surgery and its complications

I. Preoperatively, up to 1 drop 5 times during the 3 hours before surgery.

II. Postoperatively, 1 drop 3 times on the day of surgery, followed by 1 drop 3 to 5 times daily for as long as required.

- Relief of pain and photophobia; post-traumatic inflammation

I. One drop 4 to 6 hourly.

II. When pain is due to a surgical procedure (e.g. refractive surgery), 1 to 2 drops in the hour preceding surgery, 1 to 2 drops within the first 15 minutes after intervention and 1 drop 4 to 6 hourly for 3 days thereafter.

Elderly

There is no indication that the dosage needs to be modified for the elderly.

4.3 Contraindications

As with other non-steroidal anti-inflammatory agents, It is contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or by other drugs with prostaglandin synthesis inhibiting activity. There is the potential for cross-sensitivity to aspirin, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents.

4.4 Special warnings and precautions for use

The anti-inflammatory activity of ophthalmic non-steroidal anti-inflammatory agents (NSAIDs) including diclofenac may mask the onset and/or progression of ocular infections. In the presence of an infection or if there is a risk of infection, appropriate therapy should be given concurrently with Diclofenac Eye drops. Although there have been no reported adverse events, there is a theoretical possibility that patients receiving other medications which may prolong bleeding time, or with known haemostatic defects may experience exacerbation with Diclofenac Eye drops. Topical NSAIDs are known to slow or delay healing. Topical ophthalmic corticosteroids may slow corneal wound healing. Caution should be exercised when topical NSAIDs such as diclofenac are used concomitantly with topical steroids.

Eye drops are not for injection. They should never be injected subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye. Patients with evidence of corneal epithelial breakdown should immediately discontinueuse of Diclofenac Eye drops and should be monitored closely for corneal health. Diclofenac Eye drops should not be used while wearing soft contact lenses. The lenses must be removed before application of the drops and not reinserted earlier than 15 minutes after use. The Diclofenac Eye drops contain benzalkonium chloride as a preservative which may cause eye irritation and is known to discolour soft contact lenses. The wearing of contact lenses is discouraged during treatment of an ocular inflammation.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of topical NSAIDs such as diclofenac and topical steroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications including slow or delay corneal healing, therefore caution should be used.
Concomitant use of Diclofenac eye drops with medications that prolong bleeding time may increase the risk of haemorrhage. Ocular diclofenac at 0.1% has been used safely in clinical studies in combination with antibiotics and beta-blocking agents for ocular use.

4.6 Pregnancy and lactation

Pregnancy

Category C

No reproductive toxicity studies have been conducted with Diclofenac eye drops. It should not be used during the third trimester of pregnancy, due to possible risk of premature closure of the ductus arteriosus and possible inhibition of contractions.

In addition, data from epidemiological studies suggest an increased risk of miscarriage after the use of prostaglandin synthesis inhibitors in early pregnancy.

Breast-feeding

There is insufficient information on the excretion of diclofenac in human milk after the use of Diclofenac eye drops. Following oral administration of 50 mg coated tablets (content of 10 x 5 mL bottles of Diclofenac) only traces of the active substance were detected in breast milk and in quantities so small that no undesirable effects on the infant are to be expected. Use of ocular diclofenac is not recommended during breast-feeding unless the expected benefits outweigh the possible risks.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Diclofenac on human fertility. Animal studies suggest that prostaglandins are necessary for implantation. Therefore, long-term use of NSAIDs by prescription for chronic non-reproductive disorders and continuing use of over-the-counter NSAIDs preparations, while trying to conceive, could potentially adversely affect the periimplantation process and outcome.

4.7 Effects on ability to drive and use machines

Patients experiencing blurred vision or other visual disturbances should refrain from driving a vehicle or operating machines until vision clears.

4.8 Undesirable effects

The most frequently observed adverse reaction is a transient, mild to moderate eye irritation. Other less frequently observed reactions are eye pain, eye pruritus, ocular hyperaemia and blurred vision immediately after instillation of the eye drops.

Punctate keratitis or corneal disorders have been observed, usually after frequent application. In patients with risk factors of corneal disorders such as during the use of corticosteroids or with concomitant diseases such as infections or rheumatoid arthritis, diclofenac has been associated, in rare cases, with ulcerative keratitis, corneal thinning, punctate keratitis, corneal epithelium defect and corneal oedema, which might become sight-threatening. Most patients were treated for a prolonged period of time.

In rare cases dyspnoea and exacerbation of asthma have been reported.

Allergic conditions have been reported such as conjunctival hyperaemia, allergic conjunctivitis, eyelid erythema, eye allergy, eyelid oedema, eyelid pruritus, urticaria, rash, eczema, erythema, pruritus, hypersensitivity, cough and rhinitis.

Post Marketing Experience

The following adverse reactions have been reported during Alcon clinical studies with it and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 Internal Document code 4 vlo041217iNZ to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Eye disorders

Common (≥ 1% to < 10%): punctate keratitis, eye pain, eye irritation, eye pruritus, conjunctival hyperaemia.

Uncommon (≥ 0.1% to < 1%): keratitis, intraocular pressure increased, corneal oedema, conjunctival oedema, corneal deposits, conjunctival follicles, ocular discomfort, eye discharge, eyelid margin crusting, lacrimation increased, eyelid irritation, ocular hyperaemia.

Immune system disorders

Uncommon (≥ 0.1% to < 1%): hypersensitivity.

General disorders and administration site conditions

Uncommon (≥ 0.1% to < 1%): impaired healing.

The following adverse reactions have been identified from post-marketing surveillance following administration of Diclofenac eye drops. Frequency cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

Eye disorders

Not known: corneal perforation, ulcerative keratitis, corneal epithelium defect, corneal opacity, corneal thinning, allergic conjunctivitis, eye allergy, eyelid erythema, eyelid oedema, eyelid pruritus, vision blurred.

Infections and infestations

Not known: rhinitis.

Respiratory, thoracic and mediastinal disorders

Not known: asthma exacerbations, dyspnoea, cough.

Skin and subcutaneous tissue disorders

Not known: urticaria, rash, eczema, erythema, pruritus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

There is no experience of overdose with Diclofenac eye drops. However, inadvertent oral ingestion carries a minimal risk of adverse effects as a multiple dose unit of Diclofenac eye drops contains only 5 mg diclofenac sodium, corresponding to about 3%, respectively, of the recommended maximum oral daily dose for an adult.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: ophthalmologicals; anti-inflammatory agents, non-steroids,
ATC Code S01BC03.

Mechanism of action

Diclofenac eye drops contains diclofenac sodium, a non-steroidal anti-inflammatory agentwith analgesic properties. It has marked prostaglandin synthesis inhibitory activityand this is thought to have an important bearing on its mechanism of action.

Pharmacodynamic effects

Clinical trials have demonstrated that diclofenac inhibits miosis during cataract surgery and reduces ocular inflammation and pain associated with corneal epithelial defects after some types of surgical intervention. There is no indication that diclofenac has any adverse effects on wound healing. Diclofenac eye drops multiple dose unit contains a cyclodextrin, hydroxypropyl gamma- cyclodextrin (HPgamma-CD). Cyclodextrins (CDs) increase the aqueous solubility of some lipophilic water-insoluble drugs. It is believed that CDs act as true carriers by keeping hydrophobic drug molecules in solution and delivering them to the surface of biological membranes.

Clinical efficacy and safety

Not available

5.2 Pharmacokinetic properties

Results from a bioavailability study established that plasma levels of diclofenac following ocular instillation of two drops of Diclofenac Sodium Ophthalmic to each eye were below the limit of quantification (10 ng/mL) over a 4-hour period. This study suggests that limited, if any, systemic absorption occurs with Diclofenac Sodium Ophthalmic.

5.3 Preclinical safety data

Preclinical data of systemically applied diclofenac from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, teratogenicity, carcinogenicity and reproductive performance studies revealed no specific hazard for humans at the intended therapeutic doses. Systemic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors. Local ocular tolerance and toxicity of different formulations of Voltaren Ophtha were investigated and no evidence of toxicity and local adverse effects was found. The potential for local ocular toxicity and associated systemic toxicity of Voltaren Ophtha multiple dose unit (MDU) and HPgamma-CD were investigated in a series of ocular tolerance studies in rabbits. In these studies, the rabbits received up to 8 instillations of 25 microlitres of solution into the conjuctival sac of the right eye each day for up to 13 weeks. The left eye was untreated and provided a control for local effects in the treated right eye. The animals received either Voltaren Ophtha MDU with or without benzalkonium chloride or a formulation containing all of the excipients in Voltaren Ophtha MDU but containing 0.1% diclofenac potassium (instead of 0.1% diclofenac sodium) as the active ingredient or a 2% solution of HPgamma-CD in saline solution. In none of the studies was there any evidence of local adverse effects detectable by detailed ophthalmological and ocular histological examinations. There was no evidence of systemic effects in the haematology, clinical chemistry, urinalysis parameters or in the histological examination of the liver, lungs and kidneys.

Pregnancy

Systemic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. There was no evidence that diclofenac had a teratogenic potential in routine mice, rat or rabbit embryo-fetal development studies. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus *in utero* are pharmacological consequences of this class of prostaglandin synthesis inhibitors.

The prenatal, perinatal and postnatal development of the offspring were not affected.

Animal studies have so far shown no risk to the fetus during the first and second trimesters of pregnancy, but no controlled studies in pregnant women are available.

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6. Pharmaceutical particulars

6.1 List of excipients

1. Disodium EDTA BP
2. Potassium Dihydrogen Phosphate BP
3. Sodium Sulphite BP
4. Potassium Sorbate BP
5. Propylene Glycol BP
6. Sodium Hydroxide BP
7. Water for Injection BP

6.2 Incompatibilities

None known

6.3 Shelf life

36 months Unopened

1 month once opened

6.4 Special precautions

Screw the cap tightly to pierce the nozzle seal.

Use the solution within one month after first opening the container.

6.5 Warning:

1. If irritation persists or increases, discontinue the use and consult physician.
2. Do not touch the dropper tip or other dispensing tip to any surface since this may contaminate the solution.

6.6 Nature and contents of container

A clear colourless solution filled in 10 ml plastic bottle.

7. Manufacturer Name

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8. Marketing Authority

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